REMARKS

I. Status of the claims

Claims 1-7, 10, 11, 13-28, 31-34, 36-69, 71-80, 84, 85, 87-101, 104-107, 109-142, 144-151, and 153-168 are pending and stand rejected. Claims 1-7, 31, 32, 38, 39, 46, 69, 74-80, 104-1-5, 111-112, 153 and 160 have been amended, and claims 8, 9, 12, 29-30, 35, 70, 81-83, 86, 102, 103, 108, 143 and 158 have been canceled. No new matter has been added.

II. Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 1-7, 10, 11, 13-17, 25-27, 29-31, 33, 34, 36-69, 71-80, 84-91, 99, 100, 102-104, 106, 107, 109-142, 144-147 and 153-168 as being unpatentable over U.S. Patent No. 4,235,871 to Papahadjopolous et al. ("Papahadjopolous") in view of U.S. Patent No. 4,687,661 to Kikuchi et al. ("Kikuchi"), U.S. Patent No. 4,235,871 to Meers et al. ("Meers"), U.S. Patent No. 5,169,637 to Lenk et al ("Lenk"), and U.S. Patent No 6,096,335 to Thierry et al. ("Thierry"). The Examiner contends that it would have been obvious to one of skill in the art at the time of the invention to combine the water miscible solvent of Kikuchi and to use the lipid of Meers (i.e., N-acylphosphatidylethanolamines) with the teachings of Papahadjopolous. *Office action* at p. 6. The Examiner further contends that it would have been obvious to encapsulate plasmids based on the teachings of Thierry. The Examiner further contends that it would have been obvious to use ethanol or 2-propanol because Thierry and Lenk allegedly teach that these can be used to solubilize lipids. Applicants respectfully traverse.

In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 (1966). Once the Graham factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. Fed. Reg. Vol. 72, No. 195, p. 57527. The Supreme Court in *KSR* stressed that "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529.

"The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. Fed. Reg. Vol. 72, No. 195 at p. 57528.

In particular, the Examiner contends that "Papahadjopoulos taught a method of making liposomes by combining lipids . . . and nucleic acids in an inert solvent to form an emulsion, thereafter forming a gel, and finally converting the gel to a suspension of liposomes by addition of an aqueous medium." *Office Action* at p. 3.

Applicants respectfully submit that the method of Papahadjopoulos differs from the presently claimed method in several respects, and that the deficiencies of Papahadjopoulos are not remedied even in view of Kikuchi, Meers, Lenk and Thierry. Papahadjopoulos teaches that the lipids are "evaporated from their solvent on to the sides of a suitable reaction vessel." *Papahadjopoulos* at col. 4, ll. 62-64. This step is followed by the dissolution of the lipids in an inert organic solvent (which is described as solvents in which the aqueous phase does not have any appreciable solubility), and then addition of an aqueous phase containing compounds to be encapsulated. *Id.* at col. 4, l. 65-col. 5, l. 16. This produces a heterogeneous mixture, which is made into an emulsion by, for example, using a bath type sonicator. *Id.* at col. 5, ll. 42. Thus, the emulsion is formed after the aqueous phase is added. The next step in the method of Papahadjopoulos is to remove the organic solvent from the emulsion, in other words, a reverse-phase evaporation process. The evaporation step converts the mixture from an emulsion into a viscous gel. Importantly, the gel does not contain an appreciable amount of organic solvent. Addition of an aqueous buffer and agitation then converts the gel into a homogenous-appearing suspension of oliogolamellar liposomes. *Id.* at col. 6, ll. 13.

Papahadjopoulos thus differs from the present liposomes and methods in that an entirely different class of organic solvent is used, i.e., solvents with no aqueous solubility versus C1-C3 alcohols, the gel contains primarily an aqueous phase and lipids, instead of an alcohol, and the lipids are not fusogenic. Applicants submit that the differences between Papahadjopoulos and the present claims are such that, even when considering the further teachings of Kikuchi, Lenk, Meers and Thierry, one skilled in the art cannot possibly arrive at the present invention without using improper hindsight reasoning. In contrast, the present claims "directly form" the liposomes by adding an

aqueous medium to a gel, wherein the gel contains a C_1-C_3 alcohol, the lipids, and the compound to be encapsulated.

Moreover, Applicants respectfully submit that the cited documents do not render the amended claims obvious because there is no rational basis for a person skilled in the art to modify the references, as the Examiner suggests, with any reasonable expectation of success. Specifically, the claims recite that the gel comprises a C_1-C_3 alcohol. Papahadjopoulos, in contrast, ***requires*** the use of a ***water-immiscible*** organic solvent for forming "inverted micelles". *Papahadjopolous* at col. 3, ll. 48-50. An aqueous mixture containing the biologically active material for encapsulation is added to the water-immiscible organic phase to produce a 2-phase mixture that is then emulsified. It is only when the organic phase is removed from the aqueous phase that the "inverted micelles" revert to a bilayer–like structure to form large oligolamellar vesicles containing aqueous phase. *Id.* at col. 3, ll. 50-53. Papahadjopolous emphasizes that emulsification and removal of the organic phase prior to final dissolution in an aqueous phase is "essential for high capture percentage in this method and is a critical difference between the process of our invention and all previous methods described." *Id.* at col. 6, ll. 56-61. Based on these teachings, the skilled artisan would have no reasonable expectation of success in using a C_1-C_3 alcohol instead of a water immiscible organic solvent.

Kikuchi and Meers fail to overcome the deficiencies of Papahadjopolous. Kikuchi teaches that "[w]hen the drug is water-soluble and miscible with a water-soluble organic solvent . . . it is more efficient to mix it with the water-soluble organic solvent . . . ." *Kikuchi* at col. 4. ll. 3-8. Those of ordinary skill in the art know that nucleic acids are not soluble in C_1-C_3 alcohols, and would expect that the addition of a C_1-C_3 alcohol would cause the nucleic acid to come out of solution. In support of this contention, Applicants previously submitted pages from Volumes 2 and 3 of "Molecular Cloning: A Laboratory Manual," to demonstrate the precipitation of nucleic acids using ethanol and isopropanol. In response, the Examiner alleges that the reference "clearly teaches that the precipitation of nucleic acids in alcohols in performed with the addition of salt solutions." While it is true that the nucleic acids are precipitated from aqueous solution, ethanol is then used wash the product. The reference plainly states "[t]he detergent is then removed from the precipitate with ethanol (**in which the nucleic acids are insoluble**), and the nucleic acids are fully redissolved

in the buffer of choice." (emphasis added). Accordingly, Applicants maintain that Kikuchi teaches against the use of C_1-C_3 alcohols to encapsulate a nucleic acid in a liposome. Meers is relied on merely for describing n-acyl phosphatidylethanolamines, and does not provide support for the use of a C_1-C_3 alcohol, as claimed.

Applicants further respectfully remind the Examiner that a reference must be considered in its entirety, for all that it teaches, including disclosures that teach away from the claimed invention. M.P.E.P. § 2142.02. Under *KSR*, "teaching away" still provides evidence of non-obviousness. *See* 127 S.Ct. at 1745. "[P]roceeding contrary to accepted wisdom in the art is evidence of nonobviousness." M.P.E.P. §2145 (citing *in re Hedges*, 783 F.2d 1083 (Fed. Cir. 1986)). Papahadjopolous makes it clear that emulsification and removal of the water-immiscible organic solvent are required for encapsulation. Kikuchi stresses the importance of solubilizing the bioactive agent to be encapsulated in the liposome. Thus, the skilled artisan, upon reading Papahadjopolous in view of Kikuchi would be led away from the use of a C_1-C_3 alcohol as claimed because C_1-C_3 alcohols are water miscible (which is contrary to the teachings of Papahadjopoulos) and would fail to solubilize the nucleic acid (which is contrary to the teachings of Kikuchi).

The Examiner relies on Thierry for allegedly teaching "methods of making liposomes comprising lipid-nucleic acid complexes, wherein the lipids are solubilized in an alcohol having 1-4 carbon atoms . . . a nucleic acid is added to the lipids, and liposomes are formed comprising the nucleic acids." *Office Action* at p. 5. To the contrary, Thierry does not form liposomes at all. Instead, Thierry teaches that "[t]he use of conventional liposomes for DNA delivery is very limited because of the low encapsulation rate and their inability to compact large molecules such as DNA." *Thierry* at col. 2, ll. 29-32. Thierry describes "a new stable structure, which is called a Neutraplex." *Id.* at col. 10, l. 35. The Neutraplexes "have a spherical shape" with "a helical microstructure comprising coiled layers of the polyanion associated with the polar surfaces of the mixture of the cationic and anionic constituents." *Id.* at col. 10, ll. 48-52. Thus, Thierry fails to describes formation of liposomes using alcohols, as presently claimed.

Lenk is relied on for describing the use of methanol, ethanol and 2-propanol in the preparation of liposomes. *Office Action* at p. 5. But, the liposomes of Lenk encapsulate small organic molecules, not nucleic acids. As discussed above, the skilled artisan would not have been

motivated to use C1-C3 alcohols to encapsulate alcohols as claimed. Moreover, Lenk requires evaporation of the water/solvent mixture to form the liposome. *Lenk* at col. 9, ll. 45-55. The present claims, in contrast, provide a method of "directly" forming the liposomes, without an evaporation step.

For at least these reasons, Applicants respectfully submit that Papahadjopolous in view of Kikuchi, Meers, Thierry and Lenk fails to render the presently claimed methods obvious. Withdrawal of this rejection is respectfully requested.

III. Conclusion

In light of the amendments and remarks set forth above, Applicants submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims is respectfully solicited. If a telephone conference would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for timely consideration of this application be charged to **Deposit Account No. 06-1448, Reference TRA-027.01.**

Dated: October 13, 2009

Respectfully submitted,

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